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Pomegranate and type 2 diabetes

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ABSTRACT

Over the last decade, various studies have linked pomegranate (*Punica granatum* Linn), a fruit native to the Middle East, with type 2 diabetes prevention and treatment. This review focuses on current laboratory and clinical research related to the effects of pomegranate fractions (peels, flowers, and seeds) and some of their active components on biochemical and metabolic variables associated with the pathologic markers of type 2 diabetes. This review systematically presents findings from cell culture and animal studies as well as clinical human research. One key mechanism by which pomegranate fractions affect the type 2 diabetic condition is by reducing oxidative stress and lipid peroxidation. This reduction may occur by directly neutralizing the generated reactive oxygen species, increasing certain antioxidant enzyme activities, inducing metal chelation activity, reducing resistin formation, and inhibiting or activating certain transcriptional factors, such as nuclear factor κB and peroxisome proliferator–activated receptor γ. Fasting blood glucose levels were decreased significantly by punicic acid, methanolic seed extract, and pomegranate peel extract. Known compounds in pomegranate, such as punicalagin and ellagic, gallic, oleanolic, ursolic, and uallic acids, have been identified as having anti-diabetic actions. Furthermore, the juice sugar fraction was found to have unique anti-oxidant polyphenols (tannins and anthocyanins), which could be beneficial to control conditions in type 2 diabetes. These findings provide evidence for the anti-diabetic activity of pomegranate fruit; however, before pomegranate or any of its extracts can be medically recommended for the management of type 2 diabetes, controlled, clinical studies, are needed.

1. Introduction

Diabetes prevention and treatment are high priorities in medical research. Fruit extracts have been used extensively in this context because they are natural, safe, and readily available. Moreover, folk medicine suggests some possible benefits to their use. One such example of these fruits is pomegranate (*Punica granatum* Linn) (Family Punicaceae), a fruit native to the Middle East [1]. Different parts of this plant are used in indigenous Indian medicine to cure various diseases, particularly diabetes [2].

Pomegranate fractions from different parts of the fruit have been linked with the prevention and treatment of a wide range of disorders and diseases, including cardiovascular

Abbreviations: NF-κB, nuclear factor κB; ROS, reactive oxygen species; PFE, pomegranate flower extract; PPAR, peroxisome proliferator-activated receptor; LPO, lipid peroxidation; PON1, paraoxonase 1; TGs, triglycerides; ZDF rats, Zucker fatty diabetic rats; STZ rats, streptozotocin-induced diabetes rats; LDL, low density lipoprotein; HDL, high density lipoprotein; GSH, glutathione; SOD, superoxide dismutase; CAT, catalase; PSO, pomegranate seed oil.

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disease, cancer, Alzheimer disease, erectile dysfunction, male infertility, arthritis, brain ischemia, dental diseases, obesity, and diabetes [3,4]. The therapeutic potential of pomegranate fractions is due to the presence of unique bioactive compounds with antioxidant, anti-inflammatory, anti-infective, anti-atherogenic, anti-carcinogenic, and anti-hyperglycemic effects [4-6].

The connection between pomegranate and diabetes was discussed by Katz et al, 2007 [7]. Katz and his group concluded that pomegranate extracts and their active compounds could be effective in the treatment and prevention of type 2 diabetes. Later reviews that addressed the therapeutic effects of pomegranate in general [3] or the cardioprotective benefits of pomegranate juice [8] have indirectly discussed the link between pomegranate and diabetes. More recently, a review by Medjakovic and Jungbauer (2013) focused on the potential use of pomegranate and its compounds in therapy for metabolic syndrome [4].

This review summarizes studies that have evaluated pomegranates, pomegranate extracts, and its components on diabetes and related factors associated with biochemical and metabolic conditions of diabetes. The review is organized by the type of investigation conducted such as cell cultures, animal models and human clinical trials. Also, presented herein are the potential mechanisms by which the extracts of pomegranate and some of their identified components affect the conditions associated with diabetes.

1.1. *Cell culture studies*

Table 1 summarizes the in vitro studies performed on pomegranate and derived compounds and their reported effects. Nuclear factor κB (nuclear factor κ light-chain enhancer of activated B cells; NF-κB) is a protein complex that is found in almost all animal cell types and controls DNA transcription. It is involved in cellular responses to stimuli, such as reactive oxygen species (ROS), cytokines, and various forms of radiation [9]. Pomegranate wine (2.0 μg/mL) was found to inhibit the activation of NF-κB in cultured vascular-endothelial cells [10,11]. Studies performed on human acute monocytic leukemia cell line-1-differentiated macrophages showed that the traditional anti-diabetic effect of the methanolic extract of pomegranate flowers (PFE) at 500 mg kg^{-1} d^{-1} is due to the enhancement of peroxisome proliferator-activated receptor (PPAR)-γ, a transcription factor that plays an important role in carbohydrate metabolism [12]. A study performed by Parmar and Kar (2008) noted that aqueous pomegranate peel extract at 2.0 μg/mL inhibited the H_2O_2-induced lipid peroxidation (LPO) in rat red blood cells [13]. A later study showed that 1.25 to 10 μmol/L punicic acid, a conjugated linolenic acid isomer found in pomegranate, increased PPAR-α and -γ reporter activity in 3T3-L1 pre-adipocytes [14]. Koren-Gluzer et al (2011) found that pomegranate juice and 50 μmol/L punicalagin, a major polyphenol in pomegranate, increased insulin release from a β-tumor cell line, an effect similar to the activity of the paraoxonase 1 (PON1) enzyme [15]. Very recently, it has been shown that the addition of pomegranate fruit extract, rich with ellagic acid, at 50–100 μg/mL to differentiated murine 3T3-L1 adipocytes reduced the secretion and intracellular levels of resistin, an adipocytokine, by promoting its degradation at the protein level [16].

2. Rodent studies

2.1. *Effects of pomegranate peels*

A study performed on Wistar albino male rats revealed that the administration of aqueous pomegranate peel extract (200 mg/kg) reduced the concentrations of glucose in serum and LPO in cardiac, hepatic, and renal tissues [13]. The treatment of alloxan-induced diabetic rats for 10 days with 200 mg/ pomegranate peel extract, rich in polyphenols, resulted in lower fasting serum glucose and higher insulin levels as well as anti-lipid peroxidation effects [17].

2.2. *Effects of pomegranate flowers*

Pomegranate flowers have been used in Unani and Ayurvedic folk medicines to cure diabetes [18]. In 2000, a study conducted by Jafri et al on normal and alloxan-induced diabetic rats reported hypoglycemic activity (lowering blood glucose) of the aqueous-ethanolic (50%, v/v) extract (400 mg/kg) of pomegranate flowers [19]. Later, it was found that long-term oral administration of PFE (500 mg/kg) decreased the content of cardiac triglycerides (TGs) as well as plasma TGs, total

Table 1 – Cell culture studies on pomegranate fractions or phytochemicals on biochemical and metabolic variables related to type 2 diabetes

Affecter	Concentration	Effect	Target	Type of cells	References
Pomegranate wine	2.0 μg/mL	-	NF-κB	Vascular-endothelial cells	[10,11]
Pomegranate flower extract	500 mg kg^{-1} d^{-1}	+	PPAR-γ	Human acute monocytic leukemia cell line-1-differentiated macrophage cells	[12]
Pomegranate peel extract	2.0 μg/mL	-	H2O2-induced Lipid peroxidation	Rat red blood cells	[13]
Punicic acid	1.25-10 μmol/L	+	PPAR-α and -γ reporter	3T3-L1 pre-adipocytes	[14]
Punicalagin	50 μmol/L	+	Insulin	β-tumor cell line	[15]
Pomegranate fruit extract; Ellagic acid	50-100 μg/mL	-	Resistin	Differentiated murine 3T3-L1 adipocytes	[16]

(–) inhibition; (+) stimulation.

cholesterol, and fatty acids in Zucker fatty diabetic (ZDF) rats, which are considered a genetic model of obesity and type 2 diabetes. Moreover, the same research group has shown that treatment with PFE reduced the expression of cardiac mRNA encoding for PPAR-α, fatty acid transport protein, acyl-CoA oxidase, carnitine palmitoyltransferase, and 5'-AMP activated protein kinase α-2. Thus, it has been suggested that PFE prevents the increase in cardiac fatty acid uptake and oxidation in the in vivo diabetic condition [20].

Reverse transcriptase polymerase chain reaction experiments conducted by Huang et al (2005) demonstrated that PFE treatment in ZDF rats enhanced the expression of cardiac PPAR-γ mRNA and restored mRNA expression of the down-regulated cardiac glucose transporter 4. Thus, the anti-diabetic activity of PFE may result from increased insulin receptor sensitivity. This anti-diabetic activity is mostly due to the presence of gallic acid in the PFE [12]. It was found that oral administration of PFE (500 mg kg^{-1} d^{-1} for 2 weeks) improved postprandial hyperglycemia (0.5 g glucose per kg), but not fasting (20 hours) plasma glucose, in ZDF rats. The mechanism by which this change occurs could involve, in part, the inhibition of the activity of α-glucosidase [12]. Furthermore, PFE decreased cardiac fibrosis in ZDF rats, which could be due, in part, to the modulation of the NF-κB pathway and cardiac endothelin-1, a protein involved in blood vessel constriction and increased blood pressure [21].

The treatment of ZDF rats (500 mg kg^{-1} d^{-1} for 6 weeks) with the methanolic extract of pomegranate flowers inhibited the glucose loading-induced increase in plasma glucose levels while having no effect on fasting plasma glucose levels [20]. Later reports have shown that oral administration of water-soluble pomegranate flowers extract, (250 mg/kg and 500 mg/kg for 21 days) by streptozotocin-induced diabetes (STZ) rats resulted in a significant reduction in fasting blood sugar, total cholesterol, TGs, low density lipoprotein (LDL), very low-density lipoprotein, and tissue LPO levels and the elevation of high-density lipoprotein (HDL), glutathione (GSH) content, and the antioxidant enzymes glutathione reductase, glutathione peroxidase, glutathione-S-transferase, superoxide dismutase (SOD), and catalase (CAT) [22]. It has been shown that pomegranate flowers ameliorate type 2 diabetes and obesity-associated fatty liver in ZDF rats, in part by enhancing the expression of hepatic genes involved in fatty acid oxidation, such as PPAR-α, acyl-CoA oxidase, and carnitine palmitoyltransferase-1 [23]. The diethyl ether extract of pomegranate flowers at 200 mg kg^{-1} d^{-1} exhibited wound healing activity in alloxan-induced diabetic rats [24]. More recently, it has been shown that supplementation of STZ rats with pomegranate flowers at 300 to 500 mg kg^{-1} d^{-1} restored the levels of LPO and GSH towards their nondiabetic control values. Pomegranate flowers supplemented at 500 mg kg^{-1} d^{-1} reduced the increase in glial-fibrilar acidic protein content in the hippocampus of STZ rats, which is suggested to improve learning and memory performances in these animals [25].

2.3. *Effects of pomegranate seeds*

In 2001, Das et al studied the hypoglycemic activity of the methanolic seed extract of pomegranate on STZ rats; the extract, which was orally administered at 300 and 600 mg/kg, significantly decreased the level of blood glucose by 47% and 42%, respectively, after 12 hours [2]. In contrast, studies conducted by Jelodar et al (2007) on alloxan-induced diabetic rats showed that pomegranate seeds consumption (60 g kg^{-1} d^{-1} for 15 days) did not significantly reduce blood glucose [26]. These findings may due to the presence of hypoglycemic agents in pomegranate fruit that are found in high concentrations in the methanolic extract of pomegranate seeds and low concentrations in whole pomegranate seeds [26].

A study by Mcfarlin et al (2009) reported that consumption of pomegranate seed oil (PSO), rich in linolenic acid, in a period of high-fat feeding decreased weight gain and reduced the risk for type 2 diabetes in wild type CD-1 mice by improving insulin sensitivity. Moreover, the same study showed that high-fat mice supplemented with PSO had higher levels of leptin, an adipose tissue-derived hormone that is important for the regulation of both energy intake and energy expenditure, and lower levels of adiponectin, an adipose tissue-derived hormone involved in fatty acid catabolism and glucose regulation, compared to rats without PSO supplementation [27].

2.4. *Effects of pomegranate juice*

Fresh pomegranate juice contains many bioactive compounds, primarily including phenolic acids such as gallic acid, caffeic acid, chlorogenic acid, ferulic acid, and coumaric acids. It also contains non-phenolic acids, citric acid, succinic acid, malic acid, oxalic acid, and ascorbic acid [28]. The taste and acidity of pomegranate juice are mainly due to the presence of these acids. Ascorbic acid is present in approximately 10–20 mg per 100 g of juice; therefore, pomegranate juice is a good source of this antioxidant vitamin [4]. In addition, pomegranate juice contains tannins, mainly ellagitannins (such as punicalagins and granatins) and gallotannins [29-31]. The bioactivity of pomegranate in general is largely attributed to the presence of these compounds [4]. Pomegranate juice also contains flavonoids, potent antioxidants, including catechin, quercetin, and phloridzin, in addition to flavan-3-ols or flavanols (a class similar to flavonoids), primarily including catechin, epicatechin, and epigallocatechin [32]. The red color of pomegranate juice is due to anthocyanins, which are mainly present in 3-*O*-glucoside and 3, 5-*O*-diglucoside forms [33,34].

Pomegranate juice, whether freshly made or store-bought, is usually prepared by crushing the whole fruit, separating the seeds, and then filtering, pasteurizing, and concentrating the juice. The final juice concentrate is typically stored at –18°C for later use [15,35-37]. Before use, pomegranate concentrate is usually diluted to a desired concentration. In many instances, the fresh filtrate of pomegranate juice is used directly without further processing [38-40]; other times, the filtrate is dried under reduced pressure to obtain pomegranate juice extract (powder) [31,41].

The consumption of pomegranate juice sugar by diabetic mice for 10 days resulted in a significant decrease in the peritoneal macrophages total peroxide level and an increase in the cellular GSH level [42]. Mohan et al (2010) showed that pomegranate juice supplementation (100 mg/kg for 4 weeks) reduced oxidative stress (an imbalance between oxidants and antioxidants) in diabetic Wistar rats (ie, kidney and pancreas

tissues had lower levels of thiobarbituric acid reactive substances and higher activities of the antioxidant enzymes SOD, CAT, and glutathione reductase) [41]. During atherogenesis, and under oxidative stress conditions, the activity of paraoxonase 2 in macrophages is increased. Interestingly, Rozenberg et al (2006) showed that treatment of diabetic mice with pomegranate juice decreased macrophage paraoxonase 2 activity [42]. Later reports have shown that the plasma levels of stable endogenous nitric oxide end products (nitrate and nitrite) increased in rats with metabolic syndrome after treatment with pomegranate fruit extract [43]. Finally, ovariectomized mice, which represent an animal model for elevated levels of serum resistin, demonstrated a decrease in the levels of serum resistin upon the consumption of pomegranate fruit extract [16].

2.5. *Effects of pomegranate punicic acid*

Punicic acid, an omega-5 polyunsaturated fatty acid, is the main component of pomegranate seed oil. It is named for the genus of pomegranate fruit (*Punica*) [4]. Research on genetically obese db/db mice and a model of diet-induced obese mice by Hontecillas et al (2009) showed that dietary punicic acid (at 1 g/100 g of the fed diet for 30 days) decreased the level of fasting plasma glucose [14]. The plasma insulin concentrations in the same study were in line with the observed differences in plasma glucose on day 30 of the study in db/db mice. The intraperitoneal glucose test and the plasma glucose level at 0, 15, 30, 60, 90, 120, and 180 min after the injection of glucose in the same study indicated that the glucose-normalizing ability of mice fed punicic acid-supplemented diets was greater than that of the control mice [14]. Furthermore, punicic acid was found to suppress the activation of NF-κB and the expression of tumor necrosis factor-α and upregulate PPAR-α- and γ-responsive genes in the tissues controlling glucose homeostasis (skeletal muscles and adipose tissue) in these mice [14]. The loss in PPAR-γ impaired the ability of dietary punicic acid to improve the homeostasis of glucose [14]. Later reports have shown that supplementation of C57Bl/J6 mice with dietary pomegranate seed oil, rich in punicic acid, at 1 g/kg body weight per day for 12 weeks ameliorated high-fat-diet-induced obesity and insulin resistance in these mice [44].

Thiazolidinedione, or TZD, a medication used in the treatment of type 2 diabetes, acts by activating peroxisome proliferator-activated receptors specific for PPAR-γ. As with thiazolidinedione, but with no adverse side effects [45], punicic acid was found to ameliorate glucose tolerance and obesity-related inflammation in obese type 2 diabetes animal models by acting as a PPAR-γ agonist [46].

3. Human studies

Human studies connecting pomegranate with type 2 diabetes have mainly focused on the effects of pomegranate juice (Table 2). Esmaillzadeh et al (2004) found that the consumption of concentrated pomegranate juice (40 g/d for 8 weeks) significantly reduced the serum levels of total cholesterol and LDL in type 2 diabetic patients with hyperlipidemia. However, it had no significant effect on their TGs and HDL serum levels [47]. The consumption of pomegranate juice (50 mL/d for 4 months) by type 2 diabetic patients (n = 20) showed a non-significant change in fasting blood glucose, insulin, and hemoglobin A_{1c} [36]. Diabetic patients drinking pomegranate juice for three months decreased their blood's ability to oxidize *N*-linoleoyl tyrosine, a synthetic oxidative stress marker, and decreased their blood oxysterol/total cholesterol ratio by approximately 93% [48]. Later reports have concluded that pomegranate juice significantly decreased the level of LPO in type 2 diabetic patients [8]. A study on patients with non-complicated type 2 diabetes showed that pomegranate extract antagonized the hyperglycemia-induced oxidative stress, as indicated by the decrease of the plasma malondialdehyde level and the increase of the total plasma GSH level and total antioxidant capacity [49].

Paraoxonase 1, an antioxidant enzyme, is synthesized in the liver and transported in plasma in association with HDL. One important role of this enzyme is preventing the oxidation of LDL. Studies conducted by Rock et al (2008) concluded that pomegranate juice consumption may delay the development of atherosclerosis in patients with type 2 diabetes by increasing the association of PON1 with HDL and increasing its catalytic activity [36,50]. Later reports have also shown that pomegranate juice and its purified polyphenols (punicalagin, gallic acid, and ellagic acid) increase the association of recombinant PON1 to HDL in diabetic patients [35].

Table 2 – Human studies evaluating the effects of pomegranate juice on different variables in type 2 diabetic conditions

Action of pomegranate juice	Variables measured in type 2 diabetic conditions	References
-	Total cholesterol	[47]
–/+	Serum fasting glucose	[36]
–/+	Hemoglobin A_{1c}	[36]
–/+	Insulin	[36]
-	LDL; LDL oxidation	[47]
–/+	TG	[47]
–/+	HDL	[47]
-	Oxidative stress (lower *N*-linoleoyl tyrosine oxidation; lower malondialdehyde; higher GSH; higher total antioxidant capacity)	[49]
-	Blood oxysterol/total cholesterol	[48]
-	LPO	[8]
+	Association of recombinant PON1to HDL	[36,50]

(–) decrease; (+) increase; (–/+) no effect.

4. Mechanistic studies

The reports reviewed above reveal that pomegranate juice and other pomegranate extracts (peels, flowers, and seeds) are beneficial in diabetic conditions, particularly type 2 diabetes. However, the mechanism by which these fractions act is still not well understood. Moreover, the exact components

responsible for the positively reported effects are not well defined.

One apparently important mechanism by which pomegranate/extracts affect the diabetic condition is by antagonizing the damaging effects of pro-oxidants and reducing oxidative stress and lipid peroxidation. Diabetic conditions were shown to directly facilitate the production of ROS and establish a state of oxidative stress. It has been shown that the glycation reaction, which more readily occurs under hyperglycemic conditions, generates ROS [51,52]. This reaction occurs in various tissues, including the pancreas, leading to β-cell injury and the development of type 2 diabetes [53,54]. Hence, pomegranate extracts, which have potent antioxidant activity [8,33,55], may prevent (at least in part) the development of type 2 diabetes by neutralizing the generated ROS.

Indirectly, pomegranate extracts may antagonize oxidative stress by increasing the activity of certain antioxidant enzymes. For example, pomegranate juice increased the activity of the PON1 enzyme in type 2 diabetic patients [36], whereas water-soluble pomegranate flowers extract increased the activity of both SOD and CAT in diabetic rats [41]. Furthermore, some pomegranate fractions may also reduce ROS accumulation because they exhibit metal chelation activity. It has been shown that ferrous ion chelation by pomegranate juice decreases the likelihood of generating the hydroxyl radical (•OH) from hydrogen peroxide (Fenton's reaction) [42].

Type 2 diabetes has now been linked with the activation of the redox-sensitive transcription factor NF-κB [11,56]. Increased cellular levels of ROS lead to the activation of this transcriptional factor, which in turn leads to the up-regulation of a diverse array of NF-κB-controlled genes, including the endothelial tissue factor (a key factor in the coagulation cascade) [52]. Accordingly, pomegranate extracts with potent ROS scavenging activity [8,33,55], are able to inhibit the activation of NF-κB and thus diminish the development of type 2 diabetes complications, especially the cardiovascular complications. Indeed, in vitro studies performed on cultured vascular-endothelial cells confirmed that pomegranate wine is a potent inhibitor of NF-κB activation [10,11].

Pomegranate extracts also demonstrated anti-diabetic activity by affecting certain transcriptional factors involved in carbohydrate metabolism. The activators of the transcription factor PPAR-γ are commonly used to treat type 2 diabetes because they increase the sensitivity of insulin to its receptors, such as glucose transporter 4 [57,58]. Likewise, extracts from pomegranate, mainly the flowers [12,19,20], exerted an anti-diabetic effect by increasing the activity of PPAR-γ, which might be due to the gallic acid component of pomegranate flowers [12].

Type 2 diabetes is strongly associated with increased adipose tissue mass and obesity [59,60]. Resistin, a peptide-signaling molecule, is secreted by adipocytes and induced during adipogenesis (the differentiation of preadipocytes to adipocytes) [61]. Resistin neutralization has been found to enhance insulin-stimulated glucose uptake in adipocytes [61,62]. Therefore, reducing circulating resistin levels would be very beneficial for ameliorating obesity-induced insulin resistance. It has been found that the consumption of pomegranate juice and ellagic acid, a main component of pomegranate, reduced serum resistin levels in ovariectomized mice, the animal model having elevated serum resistin levels [16]. In addition, pomegranate fruit extract and ellagic acid were capable of decreasing the intracellular levels of resistin in differentiated murine 3T3-L1 adipocytes, potentially by enhancing the degradation of resistin at the protein level [16]. Consequently, the aforementioned findings suggest that drinking pomegranate juice would be very beneficial in preventing obesity-induced type 2 diabetes mellitus.

Various studies that have investigated the effect of different pomegranate fractions on fasting blood glucose, which is considered a key variable in the diagnosis of type 2 diabetes, are summarized in Table 3 [63-65]. The fasting blood glucose levels were only significantly decreased by punicic acid, methanolic seed extract, and pomegranate peel extract (Table 3). The organic fractions of pomegranate seeds are rich in punicic acid [44,66]; it might be interesting to investigate to potential of pomegranate seed extract as an anti-diabetic agent in humans. Other pomegranate components have been identified as having anti-diabetic effects,

Table 3 – Effect of different pomegranate fractions on fasting plasma or serum glucose in rodents or humans

Pomegranate fraction	Effect on fasting blood glucose	Dose-orally administered	Treatment duration	Population	References
Peels extract	-	200 mg kg^{-1} d^{-1}	10 days	Wistar albino male rats	[13,17]
Methanolic extract of flowers	–/+	500 mg kg^{-1} d^{-1}	6 weeks	Zucker fatty diabetic rats	[20]
Methanolic seed extract	-	300-600 mg/kg	At the end of 12 hours	Zucker fatty diabetic rats	[2]
Punicic acid	-	(1 g/100 g of the fed diet)	30 days	Genetically obese db/db mice	[14]
Pomegranate seeds (consumption)	–/+	60 g kg^{-1} d^{-1}	15 days	Alloxan-induced diabetic rats	[26]
Methanolic extract of flowers	–/+	500 mg kg^{-1} d^{-1}	2 weeks	Zucker fatty diabetic rats	[12]
Pomegranate juice	–/+	50 mL/d	4 months	Type 2 diabetic patients	[36]

(–) decrease; (–/+) no effect.

including punicalagin and ellagic, gallic, oleanolic, ursolic, and uallic acids [1,35,67,68].

Although pomegranate juice contains a considerable amount of sugar, it has been shown that these sugars may not worsen type 2 diabetes variables [42]. In fact, such findings are contradictory to what has been observed with other fruit juices [69]. The unique sugars in pomegranate that might be responsible for such effects have not yet been identified. Indeed, it has been reported that the sugar fraction of pomegranate juice contains antioxidant polyphenolic tannins and anthocyanins, which may contribute to the unique properties of pomegranate sugars [42]. Consequently, future studies on humans to explore the effects of the pomegranate sugar fraction on type 2 diabetes are needed.

5. Summary

Pomegranate extracts and their active components have great medical potential as they may provide an effective and safe treatment for type 2 diabetes and its pathological concerns. They affect the type 2 diabetic condition, mainly by antagonizing the damaging effects of ROS. Such a mechanism may occur directly or indirectly by increasing the activity of certain antioxidant enzymes, such as PON1, SOD, and CAT. In addition, pomegranate fractions exhibit metal chelation activity; inhibit or activate certain transcriptional factors involved in glucose normalization, such as NF-κB and PPAR-γ; and reduce resistin formation.

The levels of fasting blood glucose were only decreased by punicic acid, methanolic seed extract, and pomegranate peel extract. Known components in pomegranate (punicalagin and ellagic, gallic, oleanolic, ursolic, and uallic acids) were found to have anti-diabetic effects. Furthermore, pomegranate juice had a potential impact on type 2 diabetes variables due to its antioxidant polyphenolic tannins and anthocyanins.

Pomegranate is consumed worldwide; however, a large knowledge gap still exists regarding its use for the clinical management of type 2 diabetes. Therefore, further research on the effect of pomegranate components needs to be performed to fully characterize the relationship between this fruit and type 2 diabetes. Our lab is currently conducting a clinical study on the short-term effects of pomegranate juice consumption on fasting blood glucose and its regulating hormones.

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